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Synthesis and Primary Evaluation of the Hepatoprotective Properties of Novel Pyrimidine Derivatives

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Abstract—Based on the active ingredient of the drug Ximedon (1,2-dihydro-4,6-dimethyl-1-*N*-(2-hydroxyethyl)pyrimidone-2, referred below to as pyrimidine (**I**), novel derivatives containing biogenic acids: succinic, L-ascorbic, *para*-aminobenzoic, nicotinic, and L-2-amino-4-(methylthio)butanoic (L-methionine) acids have been synthesized. The parameters of acute toxicity (LD_{50}) have been studied. The antitoxic effect of the compounds upon the injury by the hepatotropic poison carbon tetrachloride has been examined as the primary evaluation of their hepatoprotective properties. It has been found that, according to toxicological safety, the compounds synthesized belong to classes III and IV (moderately and little toxic compounds). The conjugates of pyrimidine (**I**) with ascorbic acid and methionine (LD_{50} more than 5400 mg/kg) are least toxic. Pyrimidine (**I**) and its derivatives possess the antitoxic activity upon acute poisoning with carbon tetrachloride; the combined injection of carbon tetrachloride with pyrimidine (**I**) or its derivatives leads to an increase in the survival of animals and the normalization of the integral functional parameters, weight and body temperature, which decrease upon toxic injury. In addition, pyrimidine (**I**) and some of its derivatives (conjugates with L-ascorbic, succinic, *para*-aminobenzoic, and nicotinic acids) decrease the weight coefficients of the liver and kidneys (the organ-to-body-weight ratio) and the activity of transaminases, the markers of hepatic cytolysis, which increase upon toxic injury with carbon tetrachloride. The area of the pathological injury of the liver by steatosis and necrosis decreases by the action of pyrimidine (**I**) and its novel derivatives (conjugates with L-ascorbic, succinic, and nicotinic acids) two to three times. Advantages of pyrimidine (**I**) and its novel derivatives over the hepatoprotective drug Thiotriazolin have been revealed.

Keywords: pyrimidines, Ximedon, hepatoprotectors, liver diseases, toxic hepatitis

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INTRODUCTION

According to the data of the World Health Organization, more than two billion people in the world suffer from liver diseases. This situation requires an increasingly frequent prescription of hepatoprotectors whose main function is the prophylaxis and treatment of liver cells for injuries induced by hepatotoxins. In this connection, a search for hepatoprotectors is one of the priority problems of national public health.

Pyrimidine derivatives attract attention as potential hepatoprotectors owing to their capacity to stimulate tissue regeneration. Among pyrimidine derivatives, the drug oxymethyluracil (2-methyl-4-amino-6-oxypyrimidine) has been found to exhibit hepatoprotective properties [1]. We have shown earlier that the pyrimidine derivative 1,2-dihydro-4,6-dimethyl-1-*N*-(2-hydroxyethyl-pyrimid-2-on (compound (**I**) in Fig. 1), which is an active ingredient of the medicine Ximedon, and its L-ascorbate (compound (**III**) in Fig. 1) hold promise; they increase the adaptation reserves of the organism under stress conditions of high physical loads in the "forced swimming" test [2] and stimulate the liver regeneration after toxic injury by carbon tetrachloride [3, 4]. In addition, it has been shown that pyrimidine derivatives based on Ximedon possess a neuroprotective activity by beneficially affecting the regeneration of spinal cortex tissue after traumas [5, 6].

The aim of the present work was to study the hepatoprotective effect of novel pyrimidine derivatives of the active ingredient (**I**) of Ximedon, its salt-like conjugates with biogenic acids: succinic, L-ascorbic, *para*-aminobenzoic, nicotinic, and L-2-amino-4-(methylthio)butanoic (L-methionine) acids (com-

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Abbreviations: LD_{50}, a dose that causes the death of 50% of animals; ALT, alanine aminotransferase; AST, aspartate aminotransferase.